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COMPAZINE

Prochlorperazine (Compazine-SKF) has proved itself a useful drug in the management of overactivity and agitation in psychotic patients. It is being promoted not only for seriously disturbed patients, however, but also for the treatment of anxiety, tension and irritability as frequently encountered in office practice. It is claimed to be effective, for example, in relieving the anxiety accompanying essential hypertension, in dispelling "preoccupation with emotionally induced symptoms," and in keeping the "pregnant patient on an even emotional keel."

Compazine is a phenothiazine compound differing chemically from its sister drug chlorpromazine (Thorazine-SKF) in having a piperazinyl side chain. Though there have been reports of its successful use in cases where Thorazine has failed, the two drugs are generally similar in therapeutic action. Compazine is, however, less likely to cause drowsiness than Thorazine. Jaundice has been much less frequent with Compazine, and only two cases of agranulocytosis which may have been due to the drug have been reported.

EXTRAPYRAMIDAL SYMPTOMS - In common with trifluoperazine (Stelazine-SKF), perphenazine (Trilafon-Schering), and thiopropazate (Dartal-Searle)--all phenothiazines with similar side chains--Compazine is more likely than Thorazine to produce tremor, muscular rigidity, and other extrapyramidal manifestations. Marked restlessness and akathisia, the inability to sit still, have been reported as prominent side effects. These symptoms are often not recognized as drug effects. In one study (F. A. Freyhan, Am. J. of Psychiatry, 115:577, 1959) major or minor extrapyramidal symptoms appeared in nearly 60 per cent of hospital patients on large doses (60 to 200 mg. daily). Such symptoms are less frequent with the smaller doses used in office practice and disappear when the drug is discontinued, or when an antiparkinsonism drug is given concomitantly.

Paradoxically, the drug occasionally produces hyperactivity and agitation almost to the point of panic. Frightening extrapyramidal manifestations of the dyskinetic variety sometimes occur and may be erroneously diagnosed as encephalitis, meningitis, poliomyelitis, and even brain tumor or epilepsy. These reactions occur most frequently on the second and third day, and should be treated by intravenous or oral administration of antiparkinsonism agents. The greatest danger is that the condition will be considered an exacerbation of the anxiety process and will be treated by more drug.

COMPAZINE IN OFFICE PRACTICE - While Compazine is unquestionably effective in agitated psychotic patients, the response to the drug in the kinds of anxiety and tension frequently seen in office practice is another matter; the absence of adequate controls in most of the clinical studies of Compazine makes it impossible to know how frequently the drug is more effective than a placebo in relieving either neurotic anxiety and tension or the anxieties and tensions which are a normal reaction to many life situations. Nevertheless, when the symptoms are severe or disabling, and when older sedatives have failed, there is enough evidence to make Compazine worth trying, preferably in association with psychotherapy. It should probably be used only as a temporary adjunct; as with any tranquilizer, it should be withdrawn periodically for re-evaluation. Compazine, like other phenothiazines, is a potent antiemetic. In general, tranquilizing drugs such as Compazine appear to be least successful in the obsessive-compulsive neuroses, conversion hysteria, marked hypochondriasis, and depression--especially masked depression (C. C. Shaw and P. W. Felts, Am. J. Med. Sciences, 237:141, 1959).

Compazine is a useful drug, especially in psychotic patients, with a minimum of true toxic reactions. Unfortunately, it has a very high incidence of undesirable neurological reactions which are not due to toxicity, but are associated with the cerebral action of potent phenothiazines. Though these reactions are reversible, if unrecognized they can cause serious disability; even if recognized, they may have traumatic psychological effects. The use of Compazine in preference to the usual sedatives in the common anxiety states or for any type of mild emotional disorder cannot be recommended.

DRUG HAZARDS IN THE NEWBORN

Severe toxic effects in newborn infants, including brain damage and death, have been caused by the administration of a number of common drugs. It is now realized that the damage results from the relative inability of the newborn to detoxify, metabolize, and excrete many pharmacologic agents (N. Kretchmer, Pediatrics, 23:638, 1959). In some cases damage has resulted from administration of the drugs to the mother before or during labor.

The coupling of a potentially noxious agent with glucuronic acid is one of the body's major detoxifying mechanisms. It has recently been shown that this process only begins to develop in the first few days of life. Hence substances which in the older child and adult combine with glucuronic acid in the liver and are than excreted as glucuronides, instead remain in the newborn infant's body. Since bilirubin is normally excreted as the glucuronide, the defect in glucuronide formation may be a major factor in neonatal jaundice.

The barbiturates, morphine, chloramphenicol (Chloromycetin), sulfa drugs and water soluble vitamin K are detoxified principally as glucuronides. Failure to form glucuronide conjugates leads to a delay in excretion and frequently to the accumulation of toxic levels of drugs in the newborn. Thus, it has been shown that sulfisoxazole (Gantrisin) and high doses of water-soluble vitamin K (sodium menadione bisulfite), when given to premature infants, increase the incidence of

damage to the brain (kernicterus) by bilirubin. It is generally felt that for the newborn doses of vitamin K above 5 mg. are undesirable and not needed. Giving high doses of vitamin K to mothers before or during labor can also lead to kernicterus in the newborn.

Investigations now indicate that several other important enzymatic processes affecting the reaction to drugs are defective in the newborn infant, particularly in the premature infant. Combined with incompletely developed kidney function, these defects predispose the newborn to the accumulation of toxic levels of drugs.

Chloramphenicol has recently been found to be toxic in doses previously recommended for the newborn, and deaths have resulted in a number of hospital nurseries. The high, sustained toxic plasma levels of the drug cause diarrhea and vomiting, a marked fall in temperature and some abdominal distention; the infant becomes gray, with cold, clammy skin, and death may occur within about 18 hours. The drug should be used in the newborn with extreme caution; if it must be used, it should be administered in daily doses not exceeding 25 mg./kg. in premature infants and 50 mg./kg. in full-term infants. The producer of Chloromycetin (Parke, Davis) clearly spelled out this hazard in a letter which it recently sent to all physicians. These examples of specific toxicity illustrate the need for further investigation and for caution in drug therapy of the newborn.

ANTIPARKINSONISM DRUGS

Belladonna alkaloids have been used for the treatment of parkinsonism ever since they were first tried by Charcot in 1874. The old argument as to which of the alkaloids (scopolamine or atropine) or which of their combinations (as in stramonium, Bellabulgara, Rabellon, or Vinobel) was most effective has given way to argument over the relative merits of a variety of new synthetic drugs.

Of the post-World War II synthetics, some resemble belladonna derivatives in structure or activity. These include trihexyphenidyl (Artane, Pipanol), cycrimine (Pagitane), procyclidine (Kemadrin), caramiphen (Panparnit) and ethopropazine (Parsidol). Others are primarily antihistamines--among them diphenhydramine (Benadryl), phenindamine (Thephorin), bromodiphenhydramine (Ambodryl), and a new drug which has not yet been released, chlorphenoxamine (Phenoxene). Some combine features of both groups, like benztropine (Cogentin) and orphenadrine (Disipal). The new synthetics have largely, though not entirely, supplanted the naturally occurring belladonna alkaloids, even though many physicians feel that they have no demonstrated therapeutic superiority.

USEFULNESS OF DRUGS - Although emotional factors have a profound effect on the symptoms of parkinsonism, controls have seldom been used in studies of antiparkinsonism drugs. A recurring theme in reports on various drugs is that patients improve initially, then reach a symptomatic plateau or regress until medication is changed, or a new drug is added. This pattern has led many clinicians to believe that psychological factors related to the drug therapy are largely responsible for the benefits obtained. Despite the paucity of controlled investigations, however, most clinicians are convinced that the drugs are use-

ful. Some patients are greatly helped, some not at all; the best to be hoped for is 25 to 50 per cent improvement in symptoms. Even small improvement is often significant in terms of performance, however.

Various investigators consider some drugs (Parsidol, for example) superior for tremor, and others (Artane or Pipanol, Pagitane, Panparnit, and Kemadrin, for example) superior for rigidity. Medical Letter consultants doubt that there are any consistent, significant differences. Furthermore, when one discounts the enthusiasm of the physician for a particular drug, and the effects of such enthusiasm on the patient, it becomes difficult to single out any one drug as clearly superior therapeutically to the others. Some clinicians consulted by The Medical Letter initiate therapy with Artane or Pipanol, Kemadrin, or Benadryl, other drugs being tried as needed; they consider the choice arbitrary, however, and see no reason why other drugs should not be tried first.

With any of the drugs, therapy should be started with small doses, the dosage being gradually increased until side effects are noted, at which point dosage is reduced somewhat. If side effects become a problem, or effectiveness begins to wane, new drugs may be substituted or added; many patients take two or three different drugs simultaneously.

SIDE EFFECTS - The common undesirable effects of the anticholinergic belladonna-like drugs are dryness of the mouth, blurred vision and dizziness. Less common are nausea, epigastric distress, constipation, dysuria, nocturnal confusion, hypotension, and memory loss. Toxic psychoses and glaucoma are the most serious effects. Side effects may prevent the use of any particular drug in from 5 to 20 per cent of patients. The drowsiness which sometimes complicates antihistamine therapy is particularly undesirable because inactivity tends to aggravate rigidity. Agranulocytosis and renal injury have resulted from the use of diethazine (Diparcol), and this drug is therefore little used.

Amphetamine is frequently employed in the management of the depression which is so often encountered in parkinsonism patients. The use of reserpine or of phenothiazines, especially those with a piperazinyl side chain (see page 57) is to be avoided because these drugs may aggravate the symptoms.

DOSAGE AND COST - The following figures show typical maximum daily dosages for a number of the drugs most commonly used in parkinsonism, and the approximate daily cost to the patient. Initial dosages are, of course, much lower than those given, and doses must in all cases be individually regulated; some patients will require much less, some more, than the amounts indicated.

Drug	Daily dosage	Approximate daily cost	Drug	Daily dosage	Approximate daily cost
Artane	10 mg.	11¢	Disipal	150 mg.	33¢
Pipanol	10 mg.	11¢	Benadryl	150 mg.	11¢
Pagitane	10 mg.	18¢	Thephorin	75 mg.	11¢
Kemadrin	15 mg.	15¢	Scopolamine	2.5 mg.	8¢
Cogentin	3 mg.	10¢	Atropine	2.5 mg.	8¢
Parsidol	500 mg.	50¢			

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